# Drug News
# 藥 物 情 報

**Issue Number 64**

***This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in February 2015 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).***


## Safety Update

### Australia: Risk of inflammatory bowel disease associated with combined oral contraceptives and hormone replacement therapy

On 2 February 2015, the Therapeutic Goods Administration (TGA) had evaluated published research that describes a link between the use of combined oral contraceptives (COCs) and an increased risk of developing inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease.

During assessment of this information, the TGA identified corresponding data that suggested hormone replacement therapy (HRT) was also a potential risk factor for development of IBD. The literature also suggested that these risks may be increased in women who were smokers. The TGA found that the literature had limitations. While the research did not confirm a causal relationship and the pathogenesis of IBD remained incompletely defined, the TGA concluded that health professionals should be made aware of this information. Progestogen-only contraceptive and HRT products and products containing tibolone as the active ingredient were not specifically considered in the data evaluated, therefore the TGA could not determine whether or not those products were associated with a potential increased risk of IBD. One paper concluded that there was no difference in the IBD risk between oestrogen-only HRT products and oestrogen/progestogen combination HRT.

While the Product Information (PI) documents for most COC products include a reference to the association between these drugs and IBD, this information is not consistent across all products. The TGA is negotiating with the sponsors of COCs and oestrogen/progestogen combination HRT products to ensure adequate information is provided in their PI.

In Hong Kong, COCs and HRT products are registered pharmaceutical products. So far, the Department of Health (DH) has not received any relevant adverse reaction reports related to the drugs. The DH remains vigilant on the safety updates of the drugs.

### UK: TIOSPIR trial concluded no significant difference in mortality between tiotropium delivered via Respimat compared with Handihaler

On 12 February 2015, the Medicines and Healthcare Products Regulatory Agency (MHRA) advised healthcare professionals to take the risk of cardiovascular side effects into account when prescribing tiotropium delivered via Respimat or Handihaler to patients with certain cardiac conditions, who were excluded from clinical trials of tiotropium (including TIOSPIR). TIOSPIR clinical trial compared the safety and efficacy of tiotropium delivered via Respimat (2.5 micrograms or 5 micrograms once daily) with tiotropium delivered via HandiHaler (18 micrograms once daily), and also assessed the cardiovascular safety of the drug. TIOSPIR included 17,135 participants with chronic obstructive pulmonary disease (COPD) who were followed up for a mean of 2.3 years. A substantial number of patients with a history of cardiac disorders (1825 patients with cardiac arrhythmia and 3152 with ischaemic heart disease, coronary artery disease, or heart failure) were enrolled in the study. The study concluded that there was no significant difference in the risk

of death from any cause between tiotropium Respimat 5 micrograms or 2.5 micrograms compared with tiotropium HandiHaler. The incidences of different causes of death (including death due to cardiovascular events) and incidences of major cardiovascular adverse events were similar across the three groups. In participants with previous cardiac arrhythmia there was no significant difference in the risk of death from any cause between tiotropium Respimat 5 micrograms and tiotropium HandiHaler 18 micrograms (hazard ratio, 0.81; 95% CI, 0.58 to1.12).

When using tiotropium delivered via Respimat or Handihaler to treat COPD, healthcare professionals are advised of the following:

- take the risk of cardiovascular side effects into account for patients with conditions that may be affected by the anticholinergic action of tiotropium, including:
  - myocardial infarction in the last 6 months
  - unstable or life threatening cardiac arrhythmia
  - cardiac arrhythmia requiring intervention or a change in drug therapy in the past year
  - hospitalisation for heart failure (NYHA Class III or IV) within the past year
- tell these patients to report any worsening of cardiac symptoms after starting tiotropium
- review the treatment of all patients already taking tiotropium as part of the comprehensive management plan to ensure that it remains appropriate for them; regularly review treatment of patients at high risk of cardiovascular events
- remind patients not to exceed the recommended once daily dose

In Hong Kong, there are four registered pharmaceutical products containing tiotropium, namely Spiriva Respimat Sol for Inhal 2.5mcg (HK -57639), Spiriva Cap for Inhal 18mcg (Combopack) (HK-50663), Spiriva Cap for Inhalation 18mcg (HK-51091), and Tiotropium Bromide Powder for Inhalation 18mcg/cap (HK-63175). All of them are prescription only medicines. So far, the DH has not received any adverse drug reaction reports related to tiotropium. In view of the MHRA's announcement and the warnings on the risk of cardiovascular side effects in the UK's approved product information of tiotropium, a letter to healthcare professionals was issued on 13 February 2015 to draw their attention to the findings and warnings, and the matter will be discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/ Medicinal Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board.

## Canada: New warning on the risk of pancreatitis associated with skin-cancer drug Zelboraf (vemurafenib)

On 12 February 2015, Health Canada announced that a new warning had been added to the Canadian prescribing information for the skin-cancer drug Zelboraf (vemurafenib) advising of the risk of pancreatitis. Zelboraf is used in adults to treat a type of skin cancer (melanoma with a mutation in a specific gene) that either cannot be removed by surgery, or has spread to other parts of the body. It works by targeting proteins made from a gene called BRAF that has mutated. Zelboraf slows down or stops the growth of cancer cells.

Health Canada has completed a safety review that examined Canadian and international case reports and other data. Cases of drug-induced pancreatitis have been reported with the use of Zelboraf both in Canada and abroad. These drug reactions generally occurred in the first two weeks of Zelboraf treatment. Pancreatitis is an inflammation of the pancreas. It may range from mild discomfort to a severe, life-threatening illness. Most people with acute (sudden-onset) pancreatitis recover completely with appropriate treatment in a hospital setting. The Canadian prescribing information (product monograph) has been updated to include the risk of pancreatitis.

Healthcare professionals are advised that patients taking Zelboraf and presenting an unexplained abdominal pain should be assessed for the possibility of pancreatitis. Also, after an episode of pancreatitis, patients should be closely monitored if re-starting Zelboraf, and dose modification should be considered.

In Hong Kong, Zelboraf Film-coated Tab 240mg (HK-61970) is a registered pharmaceutical product, and is a prescription only medicine. So far, the DH has not received any adverse drug reaction reports related to the vemurafenib. In view of the Health Canada's announcement, a letter to healthcare professionals was issued on 13 February 2015 to

draw their attention to the warning, and the matter will be discussed in the meeting of the Registration Committee.

**EU: PRAC recommends measures to minimize known heart risks of hydroxyzine-containing medicines when they continue to be used.**

On 13 February 2015, the European Medicines Agency (EMA) announced that the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) had completed a review of medicines containing the antihistamine hydroxyzine. This follows concerns over the risk of possible effects on heart rhythm with these medicines, which are available in most EU countries. Their approved uses (indications) vary considerably between countries and may include use to treat anxiety disorders, for relief of pruritus (itching), as premedication before surgery, and for treatment of sleep disorders.

The PRAC considered that hydroxyzine was associated with a small but definite risk of QT interval prolongation and torsade de pointes (alterations in the electrical activity of the heart that can lead to abnormal heart rhythms and cardiac arrest). Based on the assessed data, the risk did not differ between indications, and the Committee recommended that hydroxyzine could continue to be used provided that measures to minimise the risk of problems with heart rhythm were taken.

These measures include using the medicine at the lowest effective dose for as short a time as possible. Use is not recommended in the elderly. The maximum daily dose should be no more than 100 mg in adults (50 mg in the elderly if use cannot be avoided), and 2 mg per kg body weight where used in children up to 40 kg in weight. Use must be avoided in patients who already have risk factors for heart rhythm disturbances or are taking other medicines that increase the risk of QT prolongation. Care is also needed in patients taking medicines that slow the heart rate or decrease the level of potassium in the blood, as these also increase the risk of problems with heart rhythm.

The PRAC recommendation follows a detailed review of the available evidence, which included published studies and data from regular safety monitoring, as well as consultation with experts in the treatment of children and the elderly. PRAC confirmed the known possibility of QT interval prolongation and torsade de pointes with hydroxyzine, and noted that such events were most likely to occur in patients who had risk factors. The risk can therefore be decreased by restricting hydroxyzine use in those most at risk of heart rhythm problems and reducing exposure to the medicine. The Committee recommended further study and monitoring to ensure that these measures were effective. The product information should be updated accordingly.

In Hong Kong, there are 16 registered pharmaceutical products containing hydroxyzine and they are all prescription only medicines. So far, the DH has not received any relevant adverse reaction reports related to hydroxyzine. Related news had been reported by EMA and was posted on Drug News Issue No. 55. On 16 February 2015, the DH issued letters to inform local healthcare professionals on the PRAC's recommended safety measures, which would be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) to decide the final position. On 27 March 2015, the EMA announced that the CMDh had agreed the PRAC measures by consensus. In view of the new EMA's announcement, the matter will be discussed in the meeting of the Registration Committee.

**UK: Hormone replacement therapy (HRT) and the risk of ovarian cancer**

On 13 February 2015, the MHRA had issued a statement in response to the study in The Lancet titled "Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies". The study is a meta-analysis which evaluates the association between HRT around menopause and ovarian cancer risk. The study suggests that HRT use is associated with an increased risk of the two most common types of ovarian cancer. The followings were directly copied from the MHRA:

*"Our advice has always been that the lowest effective dose of HRT should be used for the shortest possible time.*

*We will evaluate the findings of this study and its implications for shorter-term use and update product information as necessary.*

*The decision to start, continue or stop HRT should be made jointly by a woman and her doctor, based on the best advice available and her own personal circumstances, including her age, her need for treatment and her medical risk factors.*

*Women on HRT should have regular health check-ups and their need to continue treatment should be re-assessed at least annually.*

*Any woman on HRT who has any questions should speak to her doctor who is best placed to advise."*

In Hong Kong, HRT products are registered pharmaceutical products. So far, the DH has not received any relevant adverse reaction reports related to the drugs. The Drug Office remains vigilant against any new safety updates and actions adopted by other overseas health regulatory authorities for consideration of any action deemed necessary.

## Australia: Warfarin review - inclusion of important clinical information in the PI

On 17 February 2015, consumers and health professionals were advised that the TGA had completed a review of the PI for goods containing warfarin. Warfarin is an anticoagulant that is used for the prevention and treatment of problems associated with blood clots including venous thrombosis and pulmonary embolism, and some heart conditions in which blood vessels become blocked.

The review involved evaluation of the PIs and relevant medical literature, and expert advice from the Advisory Committee on the Safety of Medicines. The TGA found that the PI for warfarin required an update for clarity and inclusion of important clinical information. Proposed changes relate to potential drug interactions, patient monitoring for anticoagulant status and treatment of overdose. The TGA is working with the sponsor to update the PI to provide clearer and more up-to-date information. Further details of the proposed changes to the PI will be provided in a future alert.

Consumers are reminded that warfarin may interact with other medications, including herbal/ complementary medicines. These interactions may result in serious bleeding events. Frequent monitoring is required.

Health professionals are reminded that the safety of warfarin is maintained by frequent monitoring of the International Normalised Ratio. The major causes of bleeding with warfarin include the concomitant use of antiplatelet agents, anticoagulants and non-steroidal anti-inflammatory drugs, and concomitant use of medicines that alter the metabolism of warfarin.

In Hong Kong, there are 15 registered pharmaceutical products containing warfarin. All of them are prescription only medicines. So far, the DH has not received any adverse drug reaction reports related to warfarin. In view of the TGA's announcement that further details of the proposed changes to the PI of the products will be provided in a future alert, the DH keeps vigilant on the updates from the TGA and other overseas health authorities for consideration of any action deem necessary.

## Canada: Restriction of risperidone's dementia indication due to higher risk of cerebrovascular adverse events

It was noted from the website of Health Canada on 23 February 2015 that Janssen Inc., in consultation with Health Canada would like to inform healthcare professionals, caregivers and patients of important updates to the indication of risperidone (Risperdal) for severe dementia. The decision to limit risperidone's indication to severe dementia of the Alzheimer type is based on a comprehensive evaluation of the safety information related to all antipsychotic drugs which indicated a higher risk of cerebrovascular adverse events in patients with the mixed or vascular dementia compared to those with dementia of the Alzheimer type. The indication for risperidone in dementia has been updated and restricted to the short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. The indication no longer includes the treatment of other types of dementia such as vascular and mixed types of dementia. This updates affect all oral risperidone products.

Physicians are advised to assess the risks and benefits of the use of risperidone in elderly patients with severe dementia of the Alzheimer type, taking into account risk predictors for stroke or existing

# Safety Update

cardiovascular comorbidities in the individual patients.

In Hong Kong, there are 77 registered pharmaceutical products containing risperidone, including Risperdal oral products registered by Johnson & Johnson (Hong Kong) Ltd. All of them are prescription only medicines. Some of the products are indicated for use in dementia. So far, the DH has not received any relevant adverse drug reaction reports related to risperidone. In view of Health Canada's announcement, a letter to healthcare professionals was issued on 23 February 2015 to draw their attention to the restriction of indication of oral risperidone, and the matter will be discussed in the meeting of the Registration Committee.

# Drug Recall

**Recall one batch of Pan-Benzathine Pen G For Inj 1.2miu/Vial (HK-45748)**

On 6 February 2015, the DH endorsed a licensed drug wholesaler, LF Asia (Hong Kong) Limited - Universal Division (LF Asia), to conduct a voluntary recall of one batch (batch number: 301299) of Pan-Benzathine Pen G For Inj 1.2miu/ Vial (HK-45748) from the market due to potential quality issue.

The DH received notification from LF Asia that the French manufacturer of the product, Laboratoires Panpharma, has reported that non-compliance with Good Manufacturing Practice (GMP) was observed by the French drug regulatory authority on the manufacturer of active pharmaceutical ingredients in mainland China. Although no specific risk has been identified so far, such non-compliance may pose potential risk to the quality of the product; and hence the recall is conducted by the French manufacturer as a precautionary measure. The above batch of product is the only available batch in the market. The DH has requested LF Asia to provide a detailed investigation report as soon as possible.

Pan-Benzathine Pen G For Inj 1.2miu/Vial containing benzathine penicillin is an antibiotic injection indicated for the treatment of infections. It can only be supplied at pharmacies under the supervision of registered pharmacist upon doctor's prescription.

According to LF Asia, 3000 vials of the affected batch were imported to Hong Kong in September 2013. Among the imported stock, around 2336 vials have been supplied to private and HA hospitals, DH clinics, private doctors and pharmacies. The remaining 664 vials are now quarantined. As on 6 February 2015, the DH had not received any adverse reports in connection with the product. The DH closely monitored the recall and a notice was released on the website of the Drug Office on the same day to alert the public of the recall.

# Drug Incident

**Public urged not to buy or consume health product with undeclared controlled drug ingredients**

On 5 February 2015, the DH appealed to members of the public not to buy or consume a product named "DETOX MAX ②" as it was found to contain controlled drug ingredients.

During DH's market surveillance, a sample of "DETOX MAX ②" was collected for analysis. Test results from the Government Laboratory showed that the product contains two undeclared controlled drug ingredients, dipyrone and diclofenac. However, the product has not been registered as a pharmaceutical product in Hong Kong.

Dipyrone and diclofenac are Part I poisons and non -steroidal anti-inflammatory drugs used to relieve pain. Their side-effects include gastrointestinal discomfort, nausea and peptic ulcers. Products containing dipyrone or diclofenac for internal use are prescription drugs and should be supplied at pharmacies under the supervision of a registered pharmacist upon doctor's prescription.

A DH spokesman strongly urged members of the public not to buy or use products of doubtful composition or from unknown sources. People who have purchased the above product should stop taking it immediately and consult healthcare professionals if they are in doubt or feeling unwell.

**Pharmacy and Poisons (Amendment) Ordinance 2015**

The Pharmacy and Poisons (Amendment) Bill 2014 was passed by the Legislative Council on 21 January 2015 and published in the Gazette (Number 5, Volume 19, Legal Supplement No. 1 (No.2)) as the Pharmacy and Poisons (Amendment) Ordinance 2015 ("Amendment Ordinance") on 30 January 2015. All provisions of the Amendment Ordinance, except section 21, section 37 and section 68, were commenced on 6 February 2015.

In particular, the following amendments to the Regulation 36B of the Pharmacy and Poisons Regulation (Cap.138A) on clinical trials and medicinal tests are highlighted for your attention:

1. A person must not conduct a clinical trial on human beings/medicinal test on animals, or cause or permit such a trial/test to be conducted, except in accordance with a Clinical Trial/Medicinal Test Certificate (CTC) issued to the person. Any person who contravenes the above commits an offence and is liable to a fine at level 2 (currently HK$5,000);
2. Provision of a sample of the product or substance is no longer required for the application;
3. The Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Committee) may, subject to any conditions it thinks fit to impose, issue a CTC which is valid for a period not exceeding 5 years; and
4. The Committee may vary the condition imposed if it thinks fit to do so, and may also cancel a CTC, suspend it for a period specified by the Committee, or issue a warning letter to the holder of the certificate if it is of the opinion that the holder of the certificate has contravened a condition of the certificate or it considers it to be in the public interest to do so.

For more details of the Amendment Ordinance, please refer to the following website of the Government of the Hong Kong Special Administrative Region:

http://www.gld.gov.hk/egazette/pdf/20151905/es1201519052.pdf

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part I poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part I poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap 137) and the maximum penalty is a $30,000 fine and one year's imprisonment for each offence.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

# *Useful Contact*

## Drug Complaint:

**Tel: 2572 2068**

**Fax: 3904 1224**

**E-mail: pharmgeneral@dh.gov.hk**

## Adverse Drug Reaction (ADR) Reporting:

**Tel: 2319 2920**

**Fax: 2186 9845**

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**Link: http://www.drugoffice.gov.hk/adr.html**

**Post:** ***Pharmacovigilance Unit,***
***Drug Office, Department of Health,***
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***The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.***